AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Previously Presented) A method of delivering a nucleic acid molecule into a mammalian eye, the method comprising contacting a scleral surface of the eye with a nucleic acid molecule having a molecular weight no greater than 150 kDa such that the nucleic acid passes through the sclera and into the interior of the eye.

2. (Previously Presented) The method of claim 1, wherein the nucleic acid has a molecular weight of at least 70 kDa.

3. (Previously Presented) The method of claim 2, wherein the nucleic acid has a molecular weight of at least 100 kDa.

4. (Previously Presented) The method of claim 3, wherein the nucleic acid has a molecular weight of at least 120 kDa.

5. (Currently Amended) A method of delivering a nucleic acid molecule into a mammalian eye, the method comprising contacting a scleral surface of the eye with a nucleic acid molecule having a molecular radius of at least 0.5 nm and a molecular weight no greater than 150 kDa so that the nucleic acid passes through the sclera and into the interior of the eye.

6. (Previously Presented) The method of claim 5, wherein the nucleic acid has a molecular radius of at least 3.2 nm.

7. (Previously Presented) The method of claim 5, wherein the nucleic acid has a molecular radius of at least 6.4 nm.

8. (Previously Presented) The method of claim 1 or 5, comprising the additional step of thinning the sclera prior to contacting the scleral surface with the nucleic acid.

9. (Previously Presented) The method of claim 8, wherein the sclera has a thickness less than 70% of its pre-thinned thickness.

10. (Previously Presented) The method of claim 9, wherein the sclera has a thickness less than 60% of its pre-thinned thickness.

11. (Previously Presented) The method of claim 1 or 5, wherein the nucleic acid is contacted with said sclera together with means for facilitating the transport of the nucleic acid through the sclera.

12. (Currently Amended) The method of claim 1 or 5, wherein the nucleic acid is delivered ~~to the sclera~~ into contact with the scleral surface by a pump.

13. (Previously Presented) The method of claim 12, wherein the pump is a mechanical or osmotic pump.

14. (Currently Amended) The method of claim 1 or 5, wherein the nucleic acid is delivered into contact with the scleral surface ~~to by sclera~~ by a microchip.

15. (Previously Presented) The method of claim 1 or 5, wherein the mammal is a human.

16. (Previously Presented) The method of claim 1 or 5, wherein the method is used to treat a retinal or choroidal disease.

17. (Previously Presented) The method of claim 16, wherein the retinal or choroidal disease is selected from the group consisting of macular degeneration, diabetic retinopathy, retinitis pigmentosa and other retinal degenerations, retinal vein occlusions, sickle cell retinopathy, glaucoma, choroidal neovascularization, retinal neovascularization, retinal edema, retinal ischemia, proliferative vitreoretinopathy, and retinopathy of prematurity.

18. (Previously Presented) The method of claim 1 or 5, wherein the nucleic acid molecule is a purified nucleic acid molecule.

19. (Cancelled)

20. (Cancelled)

21. (Previously Presented) The method of claim 1 or 5, wherein the nucleic acid, when delivered, reduces development of choroidal neovascularization.

REMARKS

Claims 1-18 and 21 presently are pending and under consideration in this application.

Claim 5 has been amended to further recite that the nucleic acid has a molecular weight no greater than 150 kDa. Support for this amendment can be found throughout the application as filed. Claims 12 and 14 have been amended to recite that the nucleic acid is delivered "into contact with the scleral surface" by either a pump (claim 12) or a microchip (claim 14). Support for this amendment can be found throughout the application as filed. Applicants believe that these amendments introduce no new matter.

Rejection of Claim 21 Under 35 U.S.C. §112, First Paragraph

According to page 2 of the Office Action, claim 21 presently stands rejected for lack of written description thereby constituting new matter. Applicants respectfully traverse this rejection.

Applicants apologize for any inconvenience, and believe that support for claim 21 can be found, for example, at page 6, lines 17-23, page 7, lines 8-10; and page 8, lines 2-4 of the application as filed. In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection of Claims 1-18 and 21 Under 35 U.S.C. §112, First Paragraph

According to pages 3-4 of the outstanding Office Action, claims 1-18 and 21 presently stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Office Action alleges that the specification fails to enable one skilled in the art to practice the claimed invention. Specifically, the Office Action states that "[s]ince the instant specification does not offer specific guidance to one skilled in the art with regard to specific nucleic acid molecules that could be used in the instantly claimed methods to produce a therapeutic effect or for diagnostic use, the specification fails to enable the full scope of the claimed invention." Applicants respectfully traverse this rejection for the following reasons.

The test for enablement is whether persons skilled in the art can make and use the invention without undue experimentation (see, for example, MPEP 2164.01 and MPEP 2164.02). Applicants submit that the claims are not unduly broad and that the skilled artisan, after reading the instant application, would be fully enabled to carry out the claimed methods of contacting the sclera with a nucleic acid having a molecular weight no greater than 150 kDa.

Applicants submit that the specification provides a detailed description of how to apply a therapeutic or diagnostic agent, for example, a nucleic acid molecule, to the outer surface of the eye for transfer through the sclera, and to methods for actually detecting transfer of molecules of interest through the sclera (see, for example, the paragraph bridging pages 11 and 12, and Examples 1-5 and 8). Specifically, Applicants submit that the skilled artisan using, for example, the in vitro diffusion apparatus and the associated protocol described for Example 1 can readily determine -- without any undue experimentation whatsoever -- whether a nucleic acid having a molecular weight no greater than 150 kDa can pass through scleral tissue.

The Office appears to be concerned that the specification does not disclose a particular nucleic acid that could be used in the claimed method for therapeutic or diagnostic purposes. Applicants submit that the claimed delivery method has general applicability and need not be limited to a particular nucleic acid molecule. Applicants have made a valuable contribution to the art of ocular drug delivery and to limit the invention to a particular nucleic acid sequence would render the claims essentially worthless.

Moreover, Applicants respectfully submit that the courts have long held that "the number and variety of examples [in the specification] are irrelevant if the disclosure is "enabling" and sets forth the 'best mode contemplated.'" In re Borkowski *et al.* (CCPA 1970) 442 F2d 904, 164 USPQ 642. Applicants submit that the specification clearly discloses how to apply a nucleic acid to a scleral surface. This is all that is required by the claimed invention. However, Applicants have already provided evidence (see, Amendment and Response dated November 20, 2002) showing that the claimed method is operable. Applicants submitted to the Office a poster co-authored by Dr. Anthony Adamis (a co-inventor of the claimed invention), which was presented at the annual meeting of the Association for Research in Vision and Ophthalmology in 2002 (already of record as C3). Applicants further submit an article co-authored by Dr. Adamis

(*Investigative Ophthalmology & Visual Science*, 44:290-299, 2003; identified as article C18 in the enclosed PTO-1449 form). Both the poster and article disclose that an exemplary nucleic acid molecule (an anti-Vascular Endothelial Growth Factor (VEGF) aptamer known as EYE001) when disposed on a scleral surface of a rabbit eye in accordance with the principles disclosed in the instant application, can pass through the sclera and exert a biological effect. The aptamer EYE001 has a molecular weight of about 50 kDa. Thus, the poster and article confirm that Applicant's method can be used to deliver a nucleic acid molecule having the claimed characteristics into the interior of the eye.

During the April 29, 2003 interview, the Examiner indicated to the undersigned that it may be instructive to know whether, as of the effective filing date of the instant application (i.e., before January 5, 1999), skilled artisans would have even been motivated to administer nucleic acids into the eye for diagnostic and/or therapeutic applications. A cursory review of the literature clearly indicates that those skilled in the art were motivated to administer nucleic acids into the eye.

The Examiner is directed to articles C9 through C17 made of record in the enclosed Information Disclosure Statement and PTO-1449 form. By way of example, intravitreal injection of anti-sense oligonucleotides, ISIS 13312 and ISIS 2922, may be used to manage cytomeglovirus retinitis, an opportunistic infection affecting people with advanced HIV disease (see, for example, the articles identified as C9 through C15 in the enclosed PTO-1449 form). Furthermore, it was found that a oligonucleotide, when injected intravitreally, can inhibit retinal neovascularization in a murine model of proliferative retinopathy (see, the article identified as C16 in the enclosed PTO-1449 form). In addition, it was found that an antisense oligonucleotide, when administered intravitreally into a non-human primate model may inhibit iris neovascularization (see, article identified as C17 in the enclosed PTO-1449 form). In addition, WO 97/15330 (identified as B13 in the enclosed PTO-1449 form) discloses administering of anti-sense molecules such as anti-sense vascular endothelial growth factor (VEGF) into the eye to treat abnormal retinal vascularization. WO 97/37542 (identified as article B14 in the enclosed PTO-1449 form) discloses gene therapy for treating proliferative vitreoretinopathy. U.S. Patent No. 5,792,751 (identified as article A99 in the enclosed PTO-1449 form) discloses the transfer

and expression of genes in cells associated with fluid spaces (e.g., the vitreous of the eye). The problem that existed before Applicants' invention was not that those skilled in the art did not know what, if any, nucleic acids could be delivered to the eye, rather they were limited by the availability of methods for delivering such nucleic acids into the eye. Applicants invention is directed to solving the delivery problem.

Finally, Applicants have amended claim 5 and, therefore, the claims depending therefrom to place an upper limit on the size of the nucleic acid molecule. The Office Action indicates that the "issue relating to the need for a device for facilitating transport of the nucleic acid across the sclera remains." For example, the Office Action refers to Matsuo *et al.*, *Biochemical and Biophysical Research Communications* 219:947-950, 1996 ("Matsuo") for the proposition that specific types of liposomes must be used for a plasmid DNA to be delivered into the eye. As discussed below, Matsuo fails to teach or suggest disposing the nucleic acid onto a scleral surface. Furthermore, as discussed in more detail below, Matsuo discloses the use of a nucleic acid molecule far larger than those recited in pending claims 1 and 5.

Applicants submit that the specification fully enables the skilled artisan to practice the full scope of the claimed invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection of Claims 1-18 and 21 Under
35 U.S.C. §112, First Paragraph

According to pages 4-5 of the outstanding Office Action, claims 1-18 and 21 presently stand rejected under 35 U.S.C. §112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was in possession of the invention. Specifically, the Office states that "Applicants assert that the method may work for a variety of nucleic acids having the claimed features. No support is offered for this assertion ... Thus, Applicants arguments are not commensurate in scope with the scope of the invention." Applicants respectfully traverse this rejection to the extent that it is maintained over the pending claims for the following reasons.

Applicants submit that it is clear from the specification that Applicants were in possession of the invention at the time the application was filed. The specification provides a written description of the claimed methods (see, for example, the second full paragraph on page 5, the paragraph bridging pages 6 and 7, the first full paragraphs of pages 9 and 13, and Example 1 of the application, as filed). Moreover, Applicants, as noted above, did provide to the Office in their submission of November 20, 2002, evidence that Applicants claimed methods are indeed operable.

With regard to claim 5, Applicants have amended claim 5 and, therefore, the claims depending therefrom to include an upper size limit of the nucleic acid. Accordingly, Applicants believe that the amend obviates the rejection of claim 5 based on the lack of an "upper limit on the size of the nucleic acid to be delivered to the interior of the eye." Applicants believe that the rejection of claim 21 has been addressed in connection with the new matter rejection. Applicants submit that the portions of the specification referred to in connection with the response to the new matter rejection clearly demonstrates that the Applicants were in possession of the claimed invention.

Applicants submit that the invention is directed to the transcleral delivery of a nucleic acid into an eye. Once inside the eye, the nucleic acid can impart its effect, as shown in the evidence submitted together with Applicant's November 20, 2002 submission. Based on the teachings appearing, for example, on pages 6, lines 17-23 and in the paragraph bridging pages 7 and 8 of the application as filed, Applicants respectfully submit that they were in possession of the invention defined by claims 16 and 17.

In view of the above, Applicants respectfully submit that they were in possession of the invention as claimed, and that this rejection be reconsidered and withdrawn.

Rejection of Claims 1-18 and 21 Under
35 U.S.C. §112, Second Paragraph

According to page 5 of the outstanding Office Action, claims 1-11, 14-18 and 21 presently stand rejected for being indefinite for omitting an essential element, namely "a pump

for facilitating transport of the nucleic acid through the sclera." Applicants respectfully traverse this rejection.

Applicants respectfully submit that a pump is not an essential element of the claimed invention. Contrary to the Office Action, Applicants submit that a pump is not necessary to facilitate the transport of the nucleic acid through the sclera. Rather, all that is required is that the nucleic acid be placed into contact with the scleral surface of the eye, upon which, the nucleic passes through the eye, for example, via diffusion. Applicants submit that it is immaterial how the nucleic acid is placed on the scleral surface. It is clear from the application that the nucleic acid may be applied to the scleral surface using a variety of approaches available to those skilled in the art. For example, as discussed in the paragraph bridging pages 11 and 12 of the instant application, the nucleic acid may be applied to the scleral surface by means of, for example, an osmotic pump, a mechanical pump, or a microchip containing reservoirs of the desired agent. Accordingly, Applicants submit that the use of a pump to place a nucleic acid onto the surface of the eye does not constitute an essential element of the claimed invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

According to page 6 of the outstanding Office Action, claims 12 and 13 presently stand rejected for being indefinite insofar as the limitations in claims 12 and 13 may conflict with those of claims 1 and 5. Applicants respectfully traverse this rejection.

Applicants have amended claims 12 (therefore claim 13 which depends from claim 12) and 14 to clarify that the nucleic acid is delivered <u>into contact with the scleral surface</u> by a pump (claim 12) or by a microchip (claim 14). Applicants believe that this amendment also obviates the grammatical error in claim 14. In view of the foregoing amendments, Applicants respectfully request that these rejections be reconsidered and withdrawn.

<u>Rejection of Claim 1-7, 11 and 18 Under 35 U.S.C. §102</u>

According to page 6 of the outstanding Office Action, claims 1-7, 11 and 18 and presently stand rejected under 35 U.S.C. §102(b) as being anticipated by Matsuo *et al.*, *Biochemical and Biophysical Research Communications* 219:947-950, 1996 ("Matsuo"). Applicants respectfully traverse this rejection for the following reasons.

It is well settled that in order for a rejection to be proper under 35 U.S.C. §102(b), each and every element of the claimed invention must appear within the four corners of a single prior art reference. Applicants respectfully submit that Matsuo fails to meet this test.

Independent claims 1 and 5, as well as the claims depending therefrom are directed to a method of delivering a nucleic acid molecule having a molecular weight *no greater than 150 kDa* into a mammalian eye by contacting a *scleral surface of the eye* with the nucleic acid molecule so that it passes through the sclera and into the interior of the eye. Applicants respectfully submit that these features are neither taught nor suggested in Matsuo.

Matsuo discloses a method of applying eye drops containing genes in "specific liposomes" to a rat's eye. The authors speculate that, "[l]iposomes might penetrate the cornea, diffuse in the intraocular fluid, and then reach the retina" (see, page 948). Contrary to the Office Action, Applicants submit that there is no teaching whatsoever of the step of *contacting a scleral surface of the eye* with a nucleic acid no greater than 150 kDa in size.

Furthermore, it appears that in their studies, Matsuo used an expression plasmid vector based on p-CMV-*beta* as described by MacGregor *et al.* in Nucleic Acid Research (17:2365, 1989; see Exhibit A). Applicants believe that the p-CMV-*beta* vector is about around 7.2 kb (see, Exhibit B). Assuming that 1 kb of double stranded DNA has a molecular weight of 660 kDa (see, Exhibit C), it appears that the molecular weight of the plasmid used by Matsuo far exceeds the molecular weight of the nucleic acid delivered according to the claimed invention.

In view of the foregoing, Applicants respectfully submit that the claimed invention is neither taught nor suggested in Matsuo. According, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection of Claim 15 Under 35 U.S.C. §103

According to page 7 of the outstanding Office Action, claim 15 presently stands rejected under 35 U.S.C. §103 as being obvious over Matsuo and Faktorovich *et al.* Nature, 347:83-86, 1990 ("Faktorovich"). Applicants respectfully traverse this rejection for the following reasons.

In establishing a prima facie case of obviousness, the Office must show that the prior art contains: (1) the motivation to modify a reference, or to combine references, to arrive at the

claimed invention, (2) a reasonable expectation of success, and (3) a teaching or suggestion of all of the claim limitations (see, MPEP 2144). Applicants respectfully submit that the applied references fail to meet these criteria.

The present invention is directed to methods of administering nucleic acids no greater than 150 kDa into the interior of the eye by contacting the nucleic acid with the scleral surface of the eye. In contrast, Matsuo teaches that a gene of interest when formulated with a specific liposome and applied in an eye drop may be transferred to retinal ganglion cells of a rat eye. As discussed previously, Matsuo fails to provide any teaching whatsoever of the step of *contacting a scleral surface of the eye* with the gene of interest.

Furthermore, Table 1 in Matsuo indicates that the composition of the liposomes used in their method has a significant effect on the transport of the gene into the eye. Applicants submit that the skilled artisan, after reading Matsuo, would have no reason to believe that a nucleic acid in the absence of a particular liposome formation would be capable of being transported into the eye. Applicants submit that such liposome formulations are not required by the claimed method. Furthermore, to the extent that Matsuo even discloses delivering genes through the sclera, Matsuo discusses delivering genes through a "surgically excised scleral window" or via "puncture [of] the anterior sclera" (see, page 948, third full paragraph). In effect, Matsuo actually teaches away from the claimed invention.

Applicants submit that Matsuo fails to provide any motivation to the skilled artisan to apply a nucleic acid to a scleral surface so as to permit the nucleic acid to pass therethrough. For the sake of argument only, even if the there were sufficient motivation to apply a nucleic acid to a scleral surface, Applicants submit that there would have been no reasonable expectation that the nucleic acid would be able to pass through the sclera.

Applicants submit that the teachings of the secondary reference, Faktorovich, fail to make up for the deficiencies in Matsuo. Faktorovich discloses that *subretinal injection* [not transceleral delivery] of the basic fibroblast growth factor (b-FGF) protein can result in the rescue of photoreceptors in rats. Faktorovich fail to teach or suggest that b-FGF can be delivered by any means other than injection. In fact, Faktorovich do not even mention that a nucleic acid

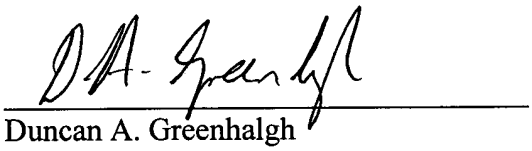
can be delivered to the eye, or that a nucleic acid having the claimed characteristics can be delivered into the eye by contacting the nucleic acid with the sclera.

Applicants respectfully submit that the claimed invention would not have been obvious to one skilled in the art at the time the invention was made based on the teachings of Matsuo, either alone or in combination, with Faktorovich. Accordingly, Applicants respectfully request that the rejection of claim 15 be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe that the application is in condition for immediate allowance. Early favorable action is respectfully solicited.

Respectfully submitted,



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